Cannabinoids, cannabis and cannabis-based medicine for pain management: a systematic review of randomised controlled trials

Abstract

Cannabinoids, cannabis and cannabis-based medicines (CBM) are increasingly used to manage pain, with limited understanding of their efficacy and safety. We summarised efficacy and adverse events of these types of drugs for treating pain using randomised controlled trials: in people of any age, with any type of pain, and for any treatment duration. Primary outcomes were 30% and 50% reduction in pain intensity, and adverse events. We assessed risk of bias of included studies, and the overall quality of evidence using GRADE. Studies of <7 and >7 days treatment duration were analysed separately. We included 36 studies (7217 participants) delivering cannabinoids (8 studies), cannabis (6 studies), and CBM (22 studies); all had high and/or uncertain risk of bias. Evidence of benefit was found for cannabis <7 days (risk difference 0.33, 95% confidence interval 0.20 to 0.46; 2 trials, 231 patients, very low-quality evidence) and nabiximols >7 days (risk difference 0.06, 95% confidence interval 0.01 to 0.12; 6 trials, 1484 patients, very low-quality evidence). No other beneficial effects were found for other types of cannabinoids, cannabis, or CBM in our primary analyses; 81% of subgroup analyses were negative. Cannabis, nabiximols, and delta-9-tetrahydrocannabinol had more adverse events than control. Studies in this field have unclear or high risk of bias, and outcomes had GRADE rating of low or very low-quality evidence. We have little confidence in the estimates of effect. The evidence neither supports nor refutes claims of efficacy and safety for cannabinoids, cannabis or CBM in the management of pain.

Summary

There is no evidence from randomised controlled trials to support or reject the use of cannabinoids, cannabis and cannabis-based medicines in the management of pain.

1.0. Introduction

Pain is a common symptom of a wide variety of common conditions, and the primary reason most patients seek health care.[41] Globally, tension type headache is the primary cause of morbidity, with musculoskeletal and neuropathic pain also common.[58] The incidence of chronic pain is routinely estimated to be between 11-40% of the population, with as many as 10% reporting high impact pain.[9; 18] Chronic pain has a larger impact on quality of life than other common chronic conditions,[70] and there is a graded increase in mortality as pain severity increases in older adults, especially for patients who report walking disability [66; 67].

Pharmacological treatments can provide considerable improvements, including reduced pain intensity and increased function. However, this benefit is limited to a minority of patients,[45] or those reporting acute pain after surgery and cancer pain.[46] These findings all relate to adult data. For children and adolescents there are little data of any kind to guide practice.[13; 14]

Cannabis plant material typically contains over 450 different compounds, with over 100 classified as phytocannabinoids. The two phytocannabinoids that have been most studied to-date in the context of medical research are delta 9-tetrahydrocannabinol (THC, the main psychoactive constituent), and cannabidiol (CBD). A large body of pre-clinical data provides evidence for antinociceptive effects of cannabinoids and modulators of the body's own endogenous cannabinoids

(endocannabinoids).[55; 71; 79] The analgesic effects of THC are mediated primarily via agonism of cannabinoid$_1$ (CB_1) and cannabinoid$_2$ (CB_2) receptors, with the former being chiefly responsible for its psychoactive effects. In contrast, CBD does not activate CB_1 or CB_2 receptors and appears to have a complex pharmacology with activity at a number of different targets which include, but are not limited to: 5-HT_{1A} receptor agonism, negative allosteric modulation of CB_1, GPR55 antagonism, TRPV1 activation, PPARγ activation, reuptake inhibition [e.g. anandamide, adenosine]).[7; 31; 36; 56; 60; 61; 73] Table 1 (adapted from Hauser et al., (2018) [27]) provides a summary of current terminology, definitions and typical products.

There is considerable research interest in the use of cannabinoids, medicinal cannabis and cannabis-based medicines (CBM), including for pain. In our recent overview review we found 57 reviews of which 49 were very low or low- quality. There is a need for a high-quality systematic review summarising the evidence.

In 2018 the International Association for Study of Pain (IASP) established a Presidential Task Force on Cannabis and Cannabinoid Analgesia to investigate the use of cannabis and cannabinoid based medicinal products for pain management. This review is part of the Task Force and aimed to provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis and CBM in clinical acute and chronic pain management, across the lifespan. We used randomized trials because they typically provide the least biased estimate for treatment efficacy. In this review, we (1) provide estimates of the efficacy and adverse events from trial data, and (2) provide an assessment of the risk of bias and quality of evidence.

2.0. Methods

2.1. Protocol Registration

We registered the protocol for this systematic review [19] and on Prospero (ID: CRD42019124714). We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[42] The aims, rationale, and methods are identical to those set out in the protocol. Where we deviated from the protocol we have noted this. This review was conducted alongside an overview review [47] and as part of the IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia.

2.2. Type of participants

We included people with acute or chronic pain. Chronic pain is defined as continuous or recurrent pain lasting for longer than three months. Acute or chronic pain includes, but was not limited to, the following conditions: abdominal pain, cancer pain, headache, migraine, acute or chronic neuropathic pain, acute or chronic musculoskeletal pain, pelvic pain, menstrual pain, acute postoperative pain, or any other form of pain. We included people with pain across the lifespan (including children). However, we excluded trials of people undergoing experimental pain procedures. We only included trials that retained 30 participants/arm at post-treatment or more. Trials that include smaller sample sizes are more likely to produce larger effects.[10; 72] However, for transparency, we have included a discussion of smaller trials in appendix 4.

2.3. Types of interventions and comparators

We included any type of cannabinoid product, natural or synthetic, delivered by any route of administration. We included any control, including placebo or active pain therapy, pharmacological or non-pharmacological. Trials that delivered cannabinoids, cannabis or CBM in addition to other drugs were also included. We only included trials that had the intention of decreasing self-reported pain intensity in participants.

2.4. Types of outcomes

We extracted the following primary and secondary outcomes:

2.4.1. Primary outcomes

1. The proportion of people with at least 30% pain intensity reduction/ moderate improvement defined by IMMPACT;[12]
2. The proportion of people with at least 50% pain intensity reduction/ substantial improvement defined by IMMPACT.[12]

2.4.2. Secondary outcomes

1. Continuous assessments of pain intensity (e.g., using a numerical rating scale or visual analogue scale);
2. The proportion of people who experienced a decrease in pain from moderate/severe to mild;
3. Disability or physical functioning;
4. Emotional functioning (e.g., anxiety, depression);
5. Carer Global Impression of Change;

6. Quality of life as defined by validated scales;
7. The number of adverse events. Adverse events will include measures of harm, including withdrawal due to serious adverse events, withdrawal because of adverse events, patients reporting any adverse event, and particular adverse events (especially CNS and cardiovascular adverse events). Following the PRISMA Harms Checklist, we will describe how adverse events were addressed, how they were reported, and over what time period the harm was experienced;[82]
8. Requirement for rescue analgesia;
9. Sleep duration and quality;
10. Onset and duration of analgesic effects (when relevant in acute pain trials).

2.5. Search method and study selection

We searched the literature using a staged approach. 1) We searched PubMed, EMBASE, and CENTRAL to April 2019 (see Appendix 1 for search strategies). We conducted a targeted search for RCTs in this area in January 2020 for any new studies. Two authors independently sifted the titles and abstracts identified in the database search. A third author resolved any disagreements. We did not restrict the searches on language or date. 2) We searched online trial registry databases including clinicaltrials.gov, EudracT. 3) We searched the trials of systematic reviews included in the overview review.[47] 4) We conducted reference and citation searches of included trials to search for further trials.

We included any peer reviewed publication or online trial registration that investigated the therapeutic effects of any cannabinoid preparation, given by any route of administration, for relief of pain, compared with placebo or a different active

treatment. We did not include trials based on the measures they reported. We did not seek other types of grey literature (e.g., unpublished dissertations) or conference abstracts.

2.6. Data extraction

Two authors independently extracted data from included trials. A third author resolved disagreements. We extracted the following data from each study:

1. Study characteristics, e.g., design, participants enrolled, age, sex, pain condition, and inclusion/exclusion criteria.
2. Intervention and comparator characteristics, e.g., type of cannabinoid, dose, route of administration, comparator.
3. Outcomes – we extracted any outcomes listed in the primary and secondary outcomes of this review. We extracted outcomes at short-term (between up to 7 days post-administration) and long-term (greater than or equal to 7 days post-administration).

2.7. Risk of bias

Two authors independently assessed the risk of bias of included studies using the Cochrane risk of bias tool [29] and a third author resolved disagreements. We assessed the following risk of bias categories, making judgements using the following criteria.[1]

[1] Please note that this section uses suggested wording from the Cochrane Pain, Palliative, and Supportive Care Review Group template, which are used in a number of Cochrane reviews (including, but not limited to [44, 75] and is unaltered from the original.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (insufficient detail about the method of randomisation to be able to judge the generation as 'low' or 'high' risk of bias). Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number) were excluded.
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (insufficient detail about the method of randomisation to be able to judge the generation as 'low' or 'high' risk of bias). Studies that do not conceal allocation (e.g. open list) were excluded.
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (no blinding or incomplete blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding, or blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken); unclear risk of bias (insufficient detail about the method of blinding to be able to judge the generation as 'low' or 'high' risk of bias, or the study does not address this

outcome), or high risk of bias (no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding, or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding).

- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (no blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding, or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken); unclear risk of bias (insufficient detail about the method of blinding to be able to judge the generation as 'low' or 'high' risk of bias, or the study does not address this); high risk of bias (no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding, or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding).
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for

missing data across groups; missing data have been imputed using 'baseline observation carried forward' analysis); unclear risk of bias (insufficient reporting of attrition/exclusions to permit a judgement of 'low risk' or 'high risk' (e.g. number randomised not stated, no reasons for missing data provided, or the study did not address this outcome); high risk of bias (reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation).

- Selective reporting (checking for reporting bias). We assessed reporting biases due to selective outcome reporting. We judged studies as: low risk of bias (the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon); unclear risk of bias (insufficient information available to permit a judgement of 'low risk' or 'high risk'); high risk of bias (not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes have been reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review have been reported incompletely so

that they cannot be entered in a meta-analysis; the study report failed to include results for a key outcome that would be expected to have been reported for such a study).

- Size (checking for possible biases confounded by small size). We assessed size of study as low risk of bias (>200 participants/arm); unclear risk of bias (50-199 participants/arm); or high risk of bias (<50 participants/arm).

2.8. Quality of the evidence[2]

We assessed the quality of the evidence using GRADE. Two review authors rated the quality of each outcome. The GRADE approach uses five considerations (study limitations, unexplained heterogeneity and inconsistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence:

- High: we are very confident that the true effect lies close to that of the estimate of the effect;
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

[2] Please note that this section uses suggested wording from the Cochrane Pain, Palliative, and Supportive Care review group template, which are used in a number of Cochrane reviews (including, but not limited to [44, 75] and is unaltered from the original.

- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Factors that may decrease the quality level of a body of evidence are:

- Limitations in the design and implementation of available studies suggesting high likelihood of bias;
- Indirectness of evidence (indirect population, intervention, control, outcomes);
- Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- Imprecision of results (wide confidence intervals);
- High probability of publication bias.

We decreased the grade rating by one (- 1) level (from high to moderate quality of evidence), two (- 2) levels (to low-quality evidence) or three (-3) levels (to very-low quality of evidence). Outcomes can be downgraded a maximum of three levels using the following criteria:

- Serious (-1) or very serious (- 2) study limitations.
- Some (- 1) or considerable (-2) inconsistency of results.
- Some (-1) or considerable (- 2) uncertainty about directness.
- Some (-1) or considerable (-2) imprecision.
- Some (-1) or considerable (-2) probability of reporting bias.

There may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines [24]. Examples might be where there are so few participants that the results are highly susceptible to the random play of chance, or if studies use last observation carried forward (LOCF) imputation in circumstances where there are substantial differences in adverse event withdrawals. In circumstances such as this there would be little confidence in the

result, which would be downgraded three levels, to very low quality. In circumstances where there are no data reported, we reported the level of evidence as very low quality.[23]

2.9. 'Summary of findings' tables

We planned to present two main 'summary of findings' tables; cannabis vs. control, and CBM (to include individual cannabinoids) vs. control. We planned to include the following seven outcomes; 50% pain reduction, 30% pain reduction, adverse events, serious adverse events, physical functioning, emotional functioning, and sleep. We rated the quality of evidence for all analyses.

2.10. Data synthesis

We combined data in meta-analyses where sufficient data were available using Revman 5.0. We used mean differences for continuous outcomes, and risk difference for dichotomous outcomes. We calculated number needed to treat to benefit (NNTB) where we were able. Heterogeneity was interpreted following the Cochrane Handbook.[30] Adverse events were entered into meta-analyses and calculated using risk differences and 95% confidence intervals. Where possible, we described any assessment of possible causality of adverse events.

We conducted comparisons of cannabis vs. control, and CBM (including individual cannabinoids) vs. control, for each of our named outcomes to determine efficacy. We conducted four primary analyses, which included all trials, conducted with a subgroup analysis by drug type, at two time-points:

1. Cannabis vs. control at short-term follow-up (up to 7 days treatment duration)

2. Cannabis vs. control at long-term follow-up (greater than or equal to 7 days treatment duration)
3. CBM vs. control at short-term follow-up (up to 7 days treatment duration)
4. CBM vs. control at long-term follow-up (greater than or equal to 7 days treatment duration).

We planned to conduct sensitivity analyses where appropriate to investigate the impact of risk of bias and study quality.

2.10.1. Subgroup analyses

In addition, where enough data were available, we conducted the following subgroup analyses at two time-points outlined above:

1. Age of participants (2-10 years, 11-17 years, 18-64 years, over 65 years);
2. Type of comparator;
3. Route of administration;
4. Dose of treatment;
5. Type of pain experienced (acute, neuropathic pain, fibromyalgia, musculoskeletal pain, headache/migraine, etc.).
6. Cannabis or CBM administered adjunctively versus non-adjunctively to other medicines.

3.0. Results

We found 8608 abstracts in the database search and 130 abstracts from other searches. After duplicates were removed, we sifted 7080 abstracts (Figure 1). We

pulled 193 full texts and subsequently excluded 129 full texts, with 36 trials meeting our inclusion criteria.

Of the 129 excluded studies, we excluded 39 studies that included fewer than 30 participants post-treatment, 27 trials that did not include people with a pain condition, 24 studies that did not assess pain as an outcome, 21 conference abstracts, two follow-up studies that were single arm, and one experimental pain study (see Appendix 2). Fifteen trials are awaiting classification; of these, three are completed, five are not yet recruiting, three are recruiting, one is ongoing, one is unknown, and two prematurely ended (no results). (see Appendix 3).

Appendix 4 describes the 39 excluded studies due to small size alone.

3.1. Included studies

The 36 completed RCTs meeting our inclusion criteria included four trial registrations without associated journal manuscripts. Across all studies, 7217 participants were randomized to trial arms and 6149 completed treatment giving an average of 14.4% attrition (0-33%). In 34 trials that reported sex, females (n = 3691) outnumbered males (3163). The average age of participants was 51 years (SD = 11). We did not find any trials including children or adolescents <18 years of age.

We found trials that treated people with neuropathic pain (n = 13), cancer (n = 6), acute pain after surgery (n = 4), multiple sclerosis (MS) (n = 10), and one each treated people with chronic prostatitis/chronic pelvic pain, carpal tunnel syndrome, and back pain.

Twenty-three trials had two arms, eight used three arms, two four arms, two five arms, and one six arms.

Trials delivered a treatment arm of nabiximols (n = 17), cannabis (n = 6), THC (n = 4; varying doses), palmitoylethanolamide (PEA; n = 3), FAAH inhibitors (n = 2; ASP3652, ASP8477), Dronabinol (n = 2), Nabilone (n = 2), cannabinoid receptor agonist (n = 2; AZD1940, GW842166), THC congener (n = 1; benzopyran peridine). A summary of trial characteristics are shown in Table 2. A more extensive description can be found in Appendix 9 and 10.

Thirty trials used only a placebo control arm. Two studies used active controls of dihydrocodeine or piritramide. Four trials delivered naproxen, ibuprofen, or codeine in addition to placebo. Most studies delivering treatments to participants with chronic pain did so in addition to on-going analgesics.

3.2. Risk of bias

Risk of bias judgments for each study are shown in Figures 2 & 3 and described in Appendix 5.

Random sequence generation (checking for possible selection bias). We judged 17 studies to be at low risk of bias for random sequence generation, and we judged the remaining studies as unclear risk of bias as they did not provide a method of randomisation.

Allocation concealment (checking for possible selection bias). Eleven studies described a convincing method of allocation concealment and were rated as low risk of bias. The remaining studies did not describe how they concealed allocation and therefore we rated them unclear.

Blinding of participants and personnel (checking for possible performance bias). We found 18 studies provided a method of blinding participants and personnel in the manuscript, which we rated as low risk of bias. The remaining studies did not

provide a clear statement of blinding, and therefore we rated these as unclear risk of bias.

Blinding of outcome assessment (checking for possible detection bias). We rated 17 studies as low risk of bias who stated a clear method of blinding outcome assessors in studies. We rated the remaining studies as unclear, as they did not provide a clear method of blinding their outcome assessors.

Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We rated 10 studies as low risk of bias for incomplete outcome data. These studies either did not report many dropouts during treatment or used baseline observation carried forwards. Twenty studies did not clearly report their data imputation method and therefore we rated these as unclear risks of bias. The remaining six studies used last observation carried forwards and therefore, we rated these studies as high risk of bias.

Selective reporting (checking for reporting bias). We found 12 studies pre-registered a protocol and reported all pre-specified outcomes in the manuscript. We found nine studies did not pre-register the protocol and rated these as unclear risk of bias. We rated 15 studies as high risk of bias; these studies pre-registered their protocol but did not report all outcomes in the manuscript or included additional outcomes in the manuscript, or have not published their results in a scientific journal.

Size. We found two studies had more than 200 participants/arm and therefore rated these as low risk of bias. A further 14 studies included between 50-200 participants/arm and judged these to be unclear risk of bias. We judged the remaining studies as high risk of bias, including fewer than 50 participants/arm.

3.3. Treatment efficacy

We found very few post-treatment means and standard deviations in treatment manuscripts and clinical registries to enter into analyses. When we requested data from authors, few replied. The authors who did respond referred us to the pharmaceutical companies, who referred us to the manuscript and clinical registry, and did not provide additional data not listed in either place. Most extractable data reported mean change from baseline.

We were unable to conduct the intended subgroup analysis due to lack of variability in the included studies. We also did not conduct sensitivity analyses by risk of bias, as most studies were either unclear or high risk of bias. Therefore, we included subgroup analyses of drug type in the primary comparisons, and also by pain condition.

We present efficacy outcomes of 30% and 50% reduction in pain intensity, and post-treatment means and standard deviations. Due to the lack of transparency caused by the inaccessibility of means and standard deviation data we decided post-protocol to also extract change from baseline means and standard deviation. Although this is selective reporting from the primary investigator, our reporting of them provides greater transparency. We report the change from baseline scores for pain below, and change from baseline means for secondary outcomes are fully described with forest plots in Appendices 6 and 7.

We report adverse events for cannabis and individual CBM, but do not report adverse events by treatment length.

We planned to present two main ‘summary of findings’ tables; cannabis vs. control, and CBM (to include individual cannabinoids) vs. control. However, due to

the lack of data for cannabis and most CBM, we only present one summary of findings table for nabiximols (Table 3).

3.3.1 Cannabis vs. control at short-term follow-up (up to 7 days treatment duration)

Three trials by one author group evaluated the effects of inhaled or vaporised cannabis on chronic neuropathic pain in single dose experiments lasting one day or less.[76-78] The studies were all three-arm trials, comparing different doses of THC content to placebo. One further study conducted a single dose crossover trial including cannabis and placebo in participants with multiple sclerosis.[6] Only one trial included participants with a minimum pain intensity score.[78]

Pain: Two trials (231 patients) reported a beneficial effect of cannabis at reducing pain intensity by at least 30% (Risk difference (RD) 0.33, 95% confidence intervals (CI) 0.20 to 0.46; very low-quality, Analysis 1.1).[76; 78] An earlier study by the same group that met inclusion also indicated short term antinociceptive effects of inhaled cannabis.[77] This would be equivalent to an NNTB of 3; the number of patients in nil effect trials required to reduce the effect to a clinically irrelevant NNTB of 10 would be 773, and to an NNTB of 20 would be 1876.

These two studies showed a short-term analgesic effect for inhaled cannabis after single doses. The size of effect (33% more patients with at least 30% pain intensity reduction) was of potential clinical significance.

One study reported continuous pain intensity post-treatment and so could not be combined in an analysis.[6] There was no difference between treatment and control for pain intensity.

Secondary outcomes: One study presented extractable data for emotional functioning.[6] However, there was no difference between groups post-treatment. Despite other outcomes assessed, we could not extract any data from the manuscripts or clinical trial.gov registration.

We downgraded GRADE ratings on all outcomes for this comparison to very low due to the small number of participants contributing to analyses, meaning we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

3.3.2 Cannabis vs. control at long-term follow-up (greater than or equal to 7 days treatment duration)

Two studies by one author group delivered cannabis treatment compared to placebo control over a 12-15 week treatment period.[80; 81] Oral capsules were delivered to participants with multiple sclerosis, and neither study defined a minimum pain intensity as part of the inclusion criteria. We could not combine any data and therefore no meta-analyses are presented.

Pain: One study with 174 participants reported 30% reduction in pain intensity and showed a proportion of the treatment group with high baseline pain reported significantly higher reduction in pain compared to placebo [81] (30% pain reduction: RR 0.19 95% CI 0.07 to 0.30, very low-quality, Analysis 2.1). However, when reporting mean pain intensity of the whole sample post-treatment, no significant effect was reported. A separate study by the same author group described a greater proportion of patients with undefined ‘improvement’ in pain for oral cannabis extract over 15 weeks, though this is difficult to interpret without understanding how the authors defined ‘improvement’.[80]

Secondary outcomes: One study reported mean sleep post-treatment and found no difference between groups.[81] No other outcomes were reported.

We downgraded all outcomes for this comparison to very low due to the small number of participants contributing to analyses.

3.3.3 CBM vs. control at short-term follow-up (up to 7 days treatment duration)

Four trials studied the effects of single dose cannabinoids on acute post-operative pain [34; 38; 54; 63] and two on cancer pain [32; 51] over the short term. A number of cannabinoids were delivered including a THC congener Benzopyran peridine,[32] a cannabinoid receptor agonist AZD1940 [34] and GW842166,[54] nabilone (a synthetic THC analog [38]) and two studies delivering different doses of THC (5- 20mg; [51; 63]). We analysed these studies together as there were too few data to analyse by CBM or cannabinoid type.

Pain: One study including 105 participants with cancer reported 30% pain reduction [32] and two studies including 207 participants with cancer reported 50% pain reduction.[32; 51] Those studies delivered a THC congener or THC respectively. Neither analysis showed differences between cannabinoid and placebo (30% pain reduction: RR 0.11 95% CI -0.09 to 0.32, very low-quality, Analysis 3.1; 50% pain reduction: RR 0.07 95% CI -0.29 to 0.43, very low-quality; Analysis 3.2). No trials of acute post-operative pain could be entered into analyses.

We were unable to combine any other data for other outcomes across these studies. One three-arm study showed no difference between AZD1904 and placebo, but participants receiving naproxen reported a significantly lower pain intensity compared to placebo after the operation.[34] A second study also failed to show any

difference between GW842166 and placebo, and ibuprofen was superior to both at reducing pain intensity.[54] Oral THC and nabilone were also without effect.[38; 63]

In conclusion, we found no analgesic effect for CBM in acute or cancer pain when treatment was delivered up to 7 days.

Secondary outcomes: One study assessed mood and found no difference between groups on anxiety post-treatment.[34]

Rescue medications were assessed in two acute pain studies.[34; 54] One study found that participants in the treatment group requested rescue medication later compared to placebo, but earlier compared to ibuprofen.[54] There was no difference between participants in the AZD1940 and placebo group requesting rescue medications.[34] However, people taking naproxen requested significantly fewer rescue medications compared to the other two groups.[34]

We could not extract data for other outcomes. We downgraded all outcomes for this comparison to very low due to the small number of participants contributing to analyses, meaning we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

3.3.4 *CBM vs. control at long-term follow-up (greater than or equal to 7 days treatment duration)*

We could combine data for nabiximols, THC, PEA and FAAH. Due to single studies delivering other types of cannabinoids, we did not combine data. Studies that did not include a minimum pain intensity are not included in these analyses. See Table 3 for quality of evidence summary of findings.

3.3.4.1 Nabiximols

We could extract data from 12 studies.[3; 16; 26; 33; 35; 39; 48; 49; 53; 57; 59; 64]

Pain: Six trials (1484 patients) have reported results for at least 30% pain relief compared with placebo in any pain condition.[33; 35; 53; 57; 59; 64] The combined effect was a small beneficial effect (RD 0.06, 95% CI 0.01 to 0.12, very low-quality evidence, Analysis 4.1.1). This would be equivalent to an NNTB of 17; the number of patients in nil effect trials required to reduce the effect to a clinically irrelevant NNTB of 20 would be 262. We downgraded this outcome twice for limitations in the design and implementation of available studies and once for indirectness of evidence.

Two trials (464 participants) have reported results for at least 50% pain relief, showing no difference from placebo (RD 0.07, 95% CI -0.04 to 0.17; very low-quality of evidence, Analysis 4.2.1).[35; 53] We downgraded this outcome due to small number of participants contributing to the analyses.

Only one study reported post-treatment means and standard deviations, and therefore we analysed mean change to be comprehensive.[59] Twelve studies (2497 patients) reported mean pain change, showing a small benefit (Mean difference (MD) -0.34, 95% CI -0.54 to -0.14; very low-quality of evidence, Analysis 4.3.1).[3; 16; 26; 33; 35; 39; 48; 49; 53; 57; 59; 64] We downgraded this outcome twice for limitations in the design and implementation of available studies and once for unexplained heterogeneity (50%).

Secondary outcomes: No studies reported post-treatment means and standard deviations for the secondary outcomes with the exception of quality of life. In one study, no differences between groups were found for quality of life outcomes.[33] Change score analyses were conducted for physical functioning,

emotional functioning, sleep and quality of life, no difference between groups was found with the exception of a significant improvement in sleep quality, favouring nabiximols. NCT01606176 reported a significant difference between the number of days using rescue analgesia, favouring the treatment group,[48] but six other trials reporting change scores found no difference between groups.

3.3.4.2 THC

Pain: We could include two trials (528 participants) in an analysis for at least 30% pain relief compared with placebo in any pain condition.[2; 33] There was no beneficial effect (RD -0.02, 95% CI -0.09, 0.05; very low-quality of evidence, Analysis 4.1.2). We downgraded this outcome to very low due to limitations in the design and implementation of available studies and indirectness of evidence. We did find any studies that reported 50% reduction of pain intensity.

One study reported post-treatment means and standard deviations so we could not analyse data (no differences reported between groups).[38] For comprehension, we also analysed mean change and found four studies (795 patients) have reported no beneficial effect of THC compared to control (MD -0.15, 95% CI -0.48 to 0.17; very low-quality, Analysis 4.3.2).[2; 3; 33; 62] We downgraded twice for limitations in the design and implementation of available studies and once for selective reporting biases.

Secondary outcomes: Two studies reported no difference in sleep quality between groups. No data could be extracted to assess other outcomes.

3.3.4.3. PEA

Pain: Two trials (744 patients) have reported results for at least 30% pain relief compared with placebo in any pain condition. The combined effect showed no benefit of PEA compared to placebo (RD 0.21, 95% CI -0.37 to 0.80; very low-quality Analysis 4.1.3).[1; 22] We downgraded once for limitations in the design and implementation and twice for heterogeneity (98%). Two trials (704 patients) have reported results for at least 50% pain relief, with no beneficial effect of PEA compared to placebo (RD 0.17, 95% CI -0.23 to 0.57, very low-quality evidence, Analysis 4.2.3).[1; 22] We downgraded both outcomes once for limitations in the design and implementation and twice for heterogeneity (>95%).

One study (78 participants) assessed post-treatment mean and standard deviations and did not find a beneficial effect of PEA compared to control.[15] Two studies (697 patients) reported mean pain change, showing no benefit (MD -0.95, 95% CI -3.14 to 1.25, very low quality, Analysis 4.3.3).[15; 22] We downgraded once for limitations in the design and implementation twice for imprecision.

Secondary outcomes: No other meta-analyses could be conducted. One study reported no differences between groups on physical functioning, emotional functioning, sleep, and quality of life.[1]

3.3.4.4. FAAH inhibitors

Pain: No studies reported 30% or 50% reduction of pain intensity. One study delivered FAAH inhibitor ASP3652 and reported post-treatment mean and standard deviations but no effect was found.[74] The same study (86 participants) reported mean change from baseline, and similarly, no beneficial effect was found between groups.[74] We downgraded both outcomes to very low due to small number of participants contributing to the analysis.

Secondary outcomes: No data were extractable for the remaining outcomes. No other CBM reported results in more than two studies.

3.3.5 Adverse events

The following analyses included all studies delivering cannabis or relevant CBM regardless of treatment length.

3.3.5.1 Cannabis

Participants with adverse events: Two studies, (750 participants) reported participants with any adverse event (AEs) and reported no difference between groups (RD 0.08, 95% CI -0.10 to 0.25, very low-quality, Analysis 5.1.1). We downgraded this outcome once for limitations in the design and implementation and twice for heterogeneity (<95%). One study reported if participants experienced a treatment-related AEs and found a significantly higher number of people receiving cannabis reported AEs compared to those in the control group.[81]

Participants with serious adverse events: Three studies (690 participants) reported no difference between groups on the number of people with serious adverse events (SAEs) overall (RD -0.05, 95% CI -0.16 to 0.07, very low-quality, Analysis 5.3.1). We downgraded this outcome once for limitations in the design and implementation and twice for heterogeneity (>75%). One study (120 participants) reported treatment-related SAEs and also found no difference between groups.

Withdrawals: Two studies (605 participants) reported all causes of withdrawal, but no difference between groups was found (RD 0.05, 95% CI -0.03 to 0.13, very low-quality, Analysis 5.5.1). We downgraded this outcome once for limitations in the design and implementation, once for indirectness, and once for heterogeneity

(>50%). Two studies also reported withdrawals due to AEs in 605 participants, and no differences was found between groups (RD 0.08, 95% CI -0.08 to 0.25, very low-quality, Analysis 5.6.1). We downgraded this outcome once for limitations in the design and implementation and twice for heterogeneity (<95%). Just one study reported withdrawal due to lack of efficacy, and similarly no difference between groups was reported. No studies reported withdrawals due to SAEs.

3.3.5.2 Nabiximols

Participants with adverse events: Twelve studies (2551 participants) reported participants in the treatment group were more likely to have an AE compared to control (RD 0.13, 95% CI 0.08 to 0.19, low-quality evidence, Analysis 5.1.2). We downgraded this outcome twice for limitations in the design and implementation of included studies. Similarly, participants in the nabiximols group were significantly more likely to report a treatment-related AE compared to control (RD 0.19, 95% CI 0.10 to 0.27, very low-quality, Analysis 5.2.2). We downgraded this outcome twice for limitations in the design and implementation of included studies and once for heterogeneity (>50%).

Participants with serious adverse events: When investigating SAEs, we found no group differences in 11 studies (2108 participants; RD 0.02, 95% CI -0.00 to 0.04, low quality, Analysis 5.3.2). We downgraded this outcome twice for limitations in the design and implementation of included studies. Similarly, in five studies with 1418 participants, no difference was found for treatment-related SAEs (RD 0.01, 95% CI -0.02 to 0.04, very low-quality, Analysis 5.4.2). We downgraded this outcome twice for limitations in the design and implementation of included studies and once for heterogeneity (>50%).

Withdrawals: Eleven studies (2489 participants) reported all causes of withdrawals and no difference was found between groups (RD 0.03, 95% CI -0.01 to 0.07, low-quality evidence, Analysis 5.5.2). We downgraded this outcome twice for limitations in the design and implementation of included studies. However, significantly more people withdrew from the treatment group due to AEs compared to control (12 studies, 2601 participants, RD 0.04, 95% CI 0.01 to 0.06, very low-quality, Analysis 5.6.2). We downgraded twice for limitations in the design and implementation of included studies and once for unexplained heterogeneity (>50%). When investigating withdrawals due to lack of efficacy (9 studies, 2001 participants) and due to SAE (5 studies, 729 participants), we did not find differences between groups (RD -0.01, 95% CI -0.02 to 0.00, Analysis 5.7.2; RD 0.00, 95% CI -0.01 to 0.02, Analysis, 5.8.1, respectively). We rated both as low-quality evidence. We downgraded the former twice for limitations in the design and implementation of included studies and the latter once for limitations in the design and implementation of included studies and once for indirectness.

3.3.5.3 THC

Participants with adverse events: We found participants in the THC arm reported more AEs compared to the control arm in four studies with 1168 participants (RD 0.15, 95% CI 0.05 to 0.24, very low-quality, Analysis 5.1.3). We downgraded this outcome once for unexplained heterogeneity (>50%) and twice for selective reporting biases. Only one study with 240 participants reported treatment-related AEs, which were significantly higher in the treatment compared to control group.

Participants with serious adverse events: Five studies reported SAEs (1012 participants) and one study reported treatment-related SAEs (240 participants). We found both analyses showed no difference between treatment and control groups (RD 0.00, 95% CI -0.02 to 0.02, low-quality, Analysis 5.3.3; RD 0.01, 95% CI -0.01 to 0.03, very low-quality, Analysis 5.4.3, respectively). We downgraded the former once for limitations in the design and implementation of included studies and once for selective reporting bias, and the latter to very low due to the small number of participants able to be included in the analysis.

Withdrawals: We found six studies (1357 participants) reported all causes of withdrawals, and no difference between groups was found (RD 0.01, 95% CI -0.06 to 0.08, very low-quality, Analysis 5.5.3). We downgraded once for limitations in the design and implementation of included studies and twice for heterogeneity. We found no differences between groups when investigating withdrawals due to AEs (7 studies, 1428 participants, RD 0.02, 95% CI -0.01 to 0.05, very low quality, Analysis 5.6.3), SAEs (4 studies, 979 participants, RD 0.00, 95% CI -0.01 to 0.01, low-quality, Analysis 5.8.2), or lack of efficacy (3 studies, 675 participants, RD 0.00, 95% CI -0.01 to 0.01, very low-quality, Analysis 5.7.3).

We downgraded withdrawals due to AEs twice for heterogeneity and once for selective reporting bias. We downgraded withdrawals due to SAEs once for indirectness and once for selective reporting bias. We downgraded withdrawals due to lack of efficacy once for limitations in the design and implementation of included studies, once for heterogeneity, and once for selective reporting bias.

3.3.5.4 PEA

Participants with adverse events: We analysed three studies (770 participants) who reported any adverse event and found no differences between groups (RD 0.03, 95% CI -0.07 to 0.14, very low-quality, Analysis 5.1.4). We downgraded once for or limitations in the design and implementation of included studies and twice for heterogeneity. No studies reported treatment-related AEs.

Participants with serious adverse events: We analysed three studies (770 participants) who reported SAEs and treatment-related SAEs and found no differences between groups for either outcomes (RD 0.02, 95% CI -0.05 to 0.08, very low-quality, Analysis 5.3.4; RD 0.00, 95% CI -0.01 to 0.01, low quality, Analysis 5.4.4). We downgraded the former outcome once for limitations in the design and implementation of included studies and twice for heterogeneity and the later outcome once for limitations in the design and implementation of included studies and once for indirectness.

Withdrawals: We analysed three studies (770 participants) who presented data for withdrawals and found no differences between groups (RD -0.03, 95% CI -0.07 to 0.01, low-quality evidence, Analysis 5.5.4). We downgraded this outcome once for limitations in the design and implementation of included studies and once for indirectness.

We could not run a meta-analysis for withdrawals due to AEs or SAEs as only one study with 73 participants reported this data. This study indicated no differences between groups. No study reported withdrawal due to lack of efficacy.

3.3.5.5 FAAH inhibitors

Participants with adverse events: A single study (238 participants) could be included when assessing participants with adverse events and treatment-related

adverse events, and there was no difference between groups in either analysis. A second EERW study reported adverse events but we did not combine data due to the different study types.[4]

Participants with serious adverse events: One EERW study reported one SAE in each group and no SAEs in either group relating to treatment.[4] A further study reported no differences for participants experiencing treatment-related SAEs.[74] The data were not combined in an analysis due to different study designs.

Withdrawals: We found two studies with different study designs report on withdrawals, but we did not combine the data. No differences were found for all causes of withdrawals. One study reported withdrawals due to AEs and found more people withdrew in the treatment compared to the control group. We could not extract any data for other withdrawal outcomes.

3.3.5.6 Cannabinoid receptor agonists

Participants with adverse events: One study (123 participants) reported any AEs and indicated no differences between groups. No studies reported AEs related to treatment.

Participants with serious adverse events: We found two studies (274 participants) reported any participants with an SAE. The analysis did not show any differences between groups (RD -0.04, 95% CI -0.22 to 0.15, very low-quality, Analysis 6.3.4). We downgraded this outcome to very low due to small number of participants that could be included in the analysis. No studies reported treatment-related SAEs.

Withdrawals: We found two studies (274 participants) reported all causes of withdrawal, withdrawals due to AEs and withdrawals due to SAEs. For all analyses,

no differences could be found between groups (RD 0.01, 95% -0.02 to 0.04, Analysis 5.5.6; RD 0.00, 95% CI -0.02 to 0.02, Analysis 5.6.6; RD 0.00, 95% CI -0.02 to 0.02, Analysis 6.8.6 respectively). We rated all three outcomes as very low-quality evidence due to the small number of participants that could be included in the analysis. On study reported withdrawals due to lack of efficacy and did not indicate any difference between groups.

3.3.6 Subgroup analyses

We analysed studies by pain condition type, irrespective of drug, dose, or route of administration; Figure 4 shows results for 30% pain intensity reduction, Figure 5 shows 50% pain intensity reduction, and Figure 6 shows mean difference (on a 0-10 scale). A description and forest plots relating to secondary outcomes can be found in Appendix 8.

3.3.6.1 Acute pain

Four trials studied the effects of single dose cannabinoids on acute pain over the short term, three on postoperative pain,[34; 54; 63] and one studied postoperative nausea and vomiting [38]. We did not find any other acute pain studies, and no data from these studies could be combined into a meta-analysis. See section 3.3.3 for a description of the results.

3.3.6.2 Cancer pain

Two trials studied the effects of THC congener or THC for cancer pain over 6 hours. [32; 51] Five trials (four studies) studied the effects of cannabinoids on cancer pain over 2 to 5 weeks, all using nabiximols. Four studies delivered nabiximols,[16;

33; 39; 57] one study also delivered THC alone.[33] Five of these studies had a minimum pain intensity of 4/10, so should have had sufficient sensitivity to detect a difference.

Pain: Pain outcomes for the two trials delivering treatment over 6 hours to participants with cancer pain are described in section 3.3.3.

Two trials delivering treatment 2-5 weeks;[33; 57] 477 participants) reported at least 30% pain relief, however, no benefit of cannabinoids were identified for reducing pain compared to placebo (RD 0.09, 95% CI -0.06 to 0.23, very low-quality, Analysis 6.1.2). We rated this outcome as very low-quality evidence due to the small number of participants that could be included in the analysis. No studies reported 50% pain reduction or pain intensity post-treatment.

Instead, four studies reported mean change from baseline (1259 participants) and findings showed no benefit of nabiximols compared to placebo (MD on a 0-10 scale -0.22, 95% CI -0.49 to 0.06, very low-quality Analysis 6.3.1;[16; 33; 39; 57]). We downgraded twice for limitations in the design and implementation of included studies and once for unexplained heterogeneity (>50%).

The second study from Fallon et al., [16] was an enriched enrolment randomised withdrawal study that found no difference between nabiximols and placebo.

Secondary outcomes: No data could be combined in an analysis for remaining outcomes. Change from baseline was reported for emotional functioning, sleep and quality of life but no differences were found in favour of CBM and declines in cognitive functioning and nausea were reported in two studies in the treatment groups.

These findings show no analgesic effect for CBM in cancer pain.

3.3.6.3 Neuropathic pain, less than 1-day cannabinoid treatment duration

The results for three trials [76-78] evaluated the effects of inhaled or vaporised cannabis (THC) on chronic neuropathic pain in single dose experiments lasting one day or less and are described in 3.3.1.

3.3.6.4 Neuropathic pain studies less than 4 weeks' treatment duration

Two studies delivered nabiximols to participants with neuropathic pain lasting one day to four weeks but did not provide data for our primary analyses.[3; 48] Both studies had a minimum pain intensity of 4/10 and should have sufficient sensitivity to detect a difference.

One study conducted a three-way crossover of nabiximols, THC, and placebo, with pain measured over the last week of a two-week treatment phase in 48 patients with brachial plexus avulsion.[3] There was a small but statistically significant reduction in mean pain score compared with placebo, with an implied 10% more patients achieving at least 30% pain intensity reduction. NCT01606176 [48] was a three-week trial of nabiximols in 70 patients with chronic refractory pain of neurological origin.[48] Both studies presented change scores and a difference between groups was found (MD -0.55, 95% CI -0.93 to -0.17, very low-quality, Analysis 6.3.2). We downgraded to very low-quality due to the small number of participants in the analysis.

No convincing analgesic effect was found for CBM in neuropathic pain in studies less than 4 weeks' duration.

Secondary outcomes: No data could be combined in an analysis for remaining outcomes. NCT01606176 reported a significant difference between the number of

days using rescue analgesia, favouring the treatment group.[48] Change data did not show any notable differences between groups.

3.3.6.5 Neuropathic pain studies; more than 4 weeks' cannabinoid treatment duration

Eight studies lasting longer than five to 15 weeks evaluated the effects of CBM in neuropathic pain (neuropathic pain in multiple sclerosis is handled separately). Of the eight studies, five delivered nabiximols, and one each delivered nabilone, PEA, or an FAAH-1 inhibitor. All studies had a minimum pain intensity of 4/10 and therefore should have sufficient sensitivity to detect a difference.

Pain: Four trials (736 participants) reported 30% pain reduction post-treatment. We found no difference between treatment and placebo groups (RD 0.03, 95% CI -0.07 to 0.12, low-quality, Analysis 6.1.5).[1; 26; 53; 64] We downgraded once for limitations in the design and implementation of included studies and once for unexplained heterogeneity. Similarly, in two trials (193 participants) that reported 50% reduction in pain intensity, we found no difference between treatment and control groups (RD 0.05, 95% CI -0.11 to 0.21, very-low quality, Analysis 5.2.5) [1; 53]. We downgraded this outcome to very low due to the small number of participants contributing to the analysis.

Only one study reported end of treatment means and standard deviations for pain intensity and showed no difference between groups.[1] Therefore, for comprehension, we extracted mean change data from baseline, reported by five studies (768 patients). We found no significant change in pain between treatment groups (MD -0.31, 95% CI -0.65 to 0.03, low-quality, Analysis 6.3.3).[1; 26; 49; 53;

64] We downgraded this outcome once for limitations in the design and implementation of included studies and once for selective reporting bias.

Two studies did not provide data for analysis. One study compared nabilone with dihydrocodeine in 96 patients with chronic neuropathic pain in a crossover study and found dihydrocodeine to be significantly better.[20] A separate study reported no difference in reduction of pain between groups.[25]

A further study used an enriched enrolment randomised withdrawal design lasting longer than four weeks in total, and with a three-week randomised withdrawal phase.[4] Due to the different study design, we describe these findings separately. The authors compared FAAH inhibitor with placebo. Of the 132 patients with peripheral neuropathic pain entering the initial phase, 71 entered the randomised withdrawal phase; there was no difference between active drug and placebo.

No convincing analgesic effect was found for CBM in neuropathic pain in studies longer than 4 weeks.

Secondary outcomes: No other meta-analyses could be conducted. One study reported no differences between groups on physical functioning, emotional functioning, sleep, and quality of life.[1] The same study reported a significantly larger number of participants in the PEA groups consumed rescue analgesia compared to the control group.[1] However, change analyses from four studies showed better sleep in participants in the treatment group compared to control, but no other analyses could be conducted.

3.3.6.6 Multiple sclerosis related chronic pain: CBM studies longer than 4 weeks

Three studies lasting five to 14 weeks examined the effects of CBM, specifically for chronic pain associated with MS.[35; 59; 62] Two studies had a minimum pain on entry of 40% of maximum, and all had mean initial pain scores of 65% of maximum or greater, so should have had sufficient sensitivity to detect a difference. Two used nabiximols, and one dronabinol and all compared to placebo control.

Pain: One study studied 339 patients taking nabiximols or placebo for 14 weeks, and provided the proportions achieving at least 30% and 50% pain intensity reduction; neither showed a benefit of nabiximols compared to placebo (Analysis 5.1.6 and 5.2.6).[35]

One study reported end of treatment means and standard deviations and showed a significant reduction in pain intensity for the treatment compared to control.[59] All three studies (613 patients) provided mean change in pain scores, and we found no difference between CBM and placebo (MD -0.41, 95% CI -1.02 to 0.19, very low-quality, Analysis 6.3.4).[35; 59; 62] We downgraded once due to unexplained heterogeneity and twice for selective reporting bias.

No convincing analgesic effect was found for CBM in neuropathic pain associated with multiple sclerosis in studies longer than 4 weeks.

Secondary outcomes: No data could be extracted for the remaining outcomes.

3.3.6.7 Multiple sclerosis studies principally examining CBM for spasticity

Six studies lasting less than one day to 15 weeks examined the effects of CBM in MS and reported some pain measures. None had a minimum pain requirement at baseline, two reported initial pain at baseline (15% and 55% of

maximum.[6; 40] Three delivered nabiximols [5; 37; 40] and three delivered cannabis extract (all with THC; [6; 80; 81]). All studies compared to placebo control.

Pain: One study with 174 participants reported 30% reduction in pain intensity and showed the treatment group reported significantly higher reduction in pain compared to placebo (Analysis 6.1.7).[81] Another study reported that 76% (n = 37) of patients with a ≥30% spasticity response also reported ≥30% reduction in pain intensity (but did not provide numbers for the placebo group).[5] A third study described a greater proportion of patients with undefined 'improvement' in pain for oral cannabis extract over 15 weeks, though this is difficult to interpret without understanding how the authors defined 'improvement'.[80]

When extracting mean pain intensity post-treatment, two studies with 337 participants [6; 81] reported no significant difference between groups.

One study found no difference between nabiximols and placebo for pain in a four-week crossover study.[37] A further study reported results of an enriched enrolment study in 107 patients over 12 weeks; mean pain was significantly lower with nabiximols than placebo.[40]

There is some evidence that CBM used to treat spasticity in multiple sclerosis also reduces pain, and there is a possibility that the two effects are linked.

Disability: In an enriched enrolment trial, no difference was found between groups for activities of daily living [40].

Emotional functioning: One study used the Brief Symptom Inventory and found no difference between groups post-treatment.[6] Another study also reported the SF-36 and reported no significant differences between groups on the mental health subscale at the end of treatment.[40]

Secondary outcomes: No other meta-analyses could be conducted.

3.3.6.8 Multiple sclerosis progression

A single study evaluated the effects of THC on slowing progression in 363 MS patients over three years.[2]

Pain: There was no significant difference in mean pain/discomfort measured by the Multiple Sclerosis Spasticity Scale-88 at any time during the study, or in the proportion feeling significantly better at the end of the study. No other outcomes were assessed.

Physical functioning: The study also reported the SF-36 “physical health” subscale but no differences were reported between groups throughout the study.

Secondary outcomes: No other meta-analyses could be conducted.

3.3.6.9 Pelvic pain

A single study examined the effects of a FAAH inhibitor to placebo on 226 participants with chronic prostatitis or pelvic pain over 12 weeks.[74] There was no minimum inclusion criteria regarding minimum reported pain intensity.

Pain: One study reported no significant differences between ASP3652 and placebo on pain intensity.[74]

Quality of life: Similarly, no differences between treatment and control were reported for quality of life outcomes.[74]

Secondary outcomes: No other meta-analyses could be conducted.

3.3.6.10 Carpal tunnel syndrome

A single study examined the effects of oral PEA to placebo in 61 patients with carpal tunnel syndrome over eight weeks.[15] There was no minimum inclusion criteria regarding minimum reported pain intensity.

Pain: There was no significant difference between PEA and placebo.

Physical functioning: There was no significant difference between PEA and placebo.

Secondary outcomes: No other meta-analyses could be conducted.

3.3.6.11 Low back pain

A single study examined the effects of oral PEA 300 mg or 600 mg in 676 patients with low back pain-sciatica, defined as “lumbosciatic algias” over three weeks,[22] with additional analyses [8]). Participants had to report a minimum pain intensity of 5/10 or equivalent to be included in the study.

Pain intensity: This study reported 50% reduction in pain intensity showing considerable benefit over placebo (Analyses 6.3.8).[22] The proportion with at least 50% pain intensity reduction with placebo was 22%, and with PEA was 58%; there was an obvious dose response, with much larger benefit with 600 mg daily. There was also a much greater reduction in average pain score with PEA (both doses combined) than placebo, again with a greater effect with 600 mg. We rated both outcomes as very low-quality as they only included one study, had limitations in the design and implementation of available studies.

This is a significant result in a large number of patients.

Physical functioning: Physical functioning was also increased in those participants in the treatment group compared to the control group. The authors found

63% of participants improved their physical functioning score in the treatment group compared to 22% in the control group.[22]

Secondary outcomes: No other meta-analyses could be conducted.

3.3.7 Potential impact of exclusion of small studies

Thirty-nine studies (794 patients given cannabinoids, cannabis, or CBM, mean 20 per trial, median 21 per trial) were excluded because of small size, potentially adding 108% additional trials but only 13% additional patients completing trials. Appendix 4 provides an analysis and details of the small excluded studies. These studies involved 12 different types of cannabis, cannabinoid or CBM in 18 different pain conditions, mostly (22/39) crossover studies. The majority (69%) used the oral route of administration, with 5 sublingual, 3 smoked, 2 inhaled, and 2 intramuscular injections. Eleven were single dose studies with duration less than one day and a further 10 lasted 1 to 14 days. There was variable reporting of outcomes.

Of the 39 trials, 22 claimed no effect of cannabis, cannabinoid or CBM, while 17 claimed some statistical benefit. Because of the small numbers potentially added to any analyses and very considerable clinical heterogeneity, the results of the main analyses in this review could not materially be altered by adding the small studies.

Discussion

This review of RCTs forms part of a wider programme of work requested by the International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia. We aimed to summarise the evidence of cannabinoids, cannabis and CBM for people with pain, examining the efficacy and adverse events reported in trials. We found 36 trials, with 7217 participants

randomized to treatment that ranged from a day to 15 weeks. Most studies investigated people with neuropathic pain or included people with pain associated with multiple sclerosis, but we also found studies investigating other pain conditions including acute post-surgical pain, cancer pain, back pain, carpal tunnel, and pelvic pain.

No study was rated as low risk of bias across all risk of bias domains; studies were rated as having unclear or high risk of bias in at least one domain, and typically in several domains. Risks of bias, high heterogeneity in some analyses, and the likelihood of selective reporting biases influenced our judgements of the quality of evidence. No outcomes achieved a higher than 'low-quality' rating. In fact, we rated most outcomes as very low-quality of evidence, meaning we are very uncertain of the estimates of effect reported.

We analyzed the efficacy of delivering cannabis (as opposed to individual cannabinoids or CBM) to people with pain and found a limited number of studies providing evidence. When assessing the effect of cannabis delivered for <1 week, two studies (231 participants) found a beneficial effect for patients undergoing surgery (very low-quality evidence). Only one study reported extractable data for cannabis delivered for >1 week, which indicated a beneficial effect of cannabis compared to control. We did not find any trials delivering cannabis for people with chronic pain that met our inclusion criteria. We found limited evidence for adverse events (1-3 studies contributing to each analysis). We found no difference between group for the adverse events analyses with the exception of treatment-related adverse events, where people in the cannabis group reported more AEs compared to the control. We found no differences for withdrawals between groups.

We found six studies that delivered CBM (including cannabinoids) to people with pain for a treatment duration of <1 week but could only extract data from two or fewer when analyzing outcomes. We did not find beneficial effects for reducing any pain intensity outcome.

We found more evidence for CBM; specifically for nabiximols delivered for >1 week treatment duration. Nabiximols showed small beneficial effects for 30% reduction in pain intensity and change in pain intensity scores (both outcomes very low-quality). THC, PEA, and FAAH inhibitors did not show beneficial effects compared to control in our primary analyses. When analyzing our secondary outcomes, we could only combine change score data for nabiximols and THC. Nabiximols showed beneficial effects for improving physical functioning in four studies and sleep quality in 13 studies. Nabiximols did not show beneficial effects for emotional functioning or quality of life, and two studies delivering THC did not show beneficial effects for sleep quality (data could not be extracted for other secondary outcomes).

We also analyzed studies by pain condition type and found no beneficial effects in favour of cannabinoids, cannabis or CBM for participants with acute pain, cancer-related pain, multiple sclerosis; we could not combine data for conditions including pelvic pain, carpal tunnel syndrome, or low back pain. We found a small benefit at reducing pain in neuropathic pain (<7 days) in two studies (very low-quality), and pain change scores for neuropathic pain (>4 weeks) in five studies (low quality) were undermined by the small size of the benefit and the likelihood of residual positive bias in the studies. Benefits of CBM (including the THC studies that did not show an improvement in sleep) were also found for improving sleep quality

for neuropathic pain of both less than and more than 4-week treatment duration (both very low-quality), although similar caveats apply.

The current available evidence provides us with no confidence that a defined cannabinoid, cannabis or CBM product, at a defined dose, using a defined route of administration, reduces pain intensity in any condition. Nor do we fully understand the long-term implications of taking cannabinoids, cannabis and CBM. Evidence is emerging on the negative long-term effects of cannabis, in particular cannabis with high THC content (>10% potency; [11]) but data for longer-term use of cannabinoids, cannabis, and CBM in a medicinal context are lacking at present. A separate work package has investigated the adverse effects of cannabis and CBM[21] and there is a distinct underreporting of adverse events in this field.[43; 68; 69] We found adverse events to be higher in nabiximols and THC treatment groups compared to control.

As is usual with systematic reviews of clinical trial evidence, we attempted to extract means and standard deviations post-treatment. These data are preferable to change scores, as successful randomization will result in no group baseline differences and therefore means/SDs can be compared at post-treatment to determine the efficacy of a treatment. However, it was not possible to extract means and standard deviations from the included studies, and when we requested data from authors, we received very few responses. Whilst one author provided partial data, and another fully responded to our request, pharmaceutical companies stated they could not provide post-treatment means and standard deviations. The lack of openness and transparency is against current best practice in science [50] and can lead one to question why data are being withheld. For the comprehensiveness of our review, we analyzed available change score data and found very few beneficial effects of cannabis or CBM.

There are still many missing areas of understanding within the evidence base, due to poorly reported trials and lack of exploration in this area. For example, we could not extract any caregiver global impression of change across the included studies. There were also very few studies reporting on the effect of physical and emotional functioning, although sleep was more consistently reported across studies.

For transparency we have described the small n studies excluded by our protocol (12 cannabinoids, cannabis, and CBM studies, 18 pain conditions, 5 routes of administration, variation in study duration of <1 to 84 days, and limitations in outcomes reported). The conclusions of the main analyses in this review could not be affected by adding the small studies. A recent systematic review reported larger effect sizes and higher uncertainty in studies with fewer than 30 participants/arm.[72] Higher effect sizes with small size is a recognized problem in systematic reviews, including systematic reviews of pain treatments.[10; 17; 44; 52]

This systematic review should be interpreted alongside the overview review of cannabinoids, cannabis and CBM.[47] That overview found 57 systematic reviews analyzing cannabis and CBMs. Those reviews were rated for quality using several indicators; the authors rated 41 as critically low, eight low quality, six as moderate, and two as high quality. Twenty-five reviews presented positive recommendations in the abstract, 12 reviews had negative recommendations, seven held equipoise, and 13 state no recommendations for or against cannabinoid, cannabis, or CBMs. We believe that this review addresses the requirements of AMSTAR-2 [65] and the critical pain criteria suggested by Moore et al [47] as far as the available trial reports allow.

Implications for research: There are many avenues for future research in this field. First, compared with the diversity of cannabinoids assessed preclinically, very

few have been investigated in clinical trials in pain, and better understanding of the analgesic effects of different compounds is needed, including both plant-derived and synthetic modulators of the endocannabinoid system. Thus, research on other cannabinoids where we did not identify any studies here, such as cannabidiol, could be explored to determine if they have any analgesic properties. Second, research should not be restricted to Western, educated, industrialized, rich, democratic (WEIRD) countries [28] and in small sample sizes. All studies came from WEIRD countries and only two studies in our review included more than 200 participants/arm and were rated as 'low risk of bias' for size. Third, coordinated, double blind, multicenter studies that include people with a minimum pain intensity of 4/10 should be carefully designed and conducted for well-defined pain conditions and at well-defined doses and routes of administration over long treatment periods. Rigorous reporting of these trials is critical to increasing the quality of evidence and confidence in the estimates of effect. Trial sponsors should register protocols, adhere to registered protocols, and make data available for scrutiny. Fourth, studies that investigate PK/PD relationships are essential.

Implications for practice: Currently, there is no evidence from RCTs to inform the practice of treating chronic pain patients with cannabinoids, cannabis or CBM to alter pain intensity, disability, emotional distress, or sleep. Although other, lower quality forms of evidence (e.g., non-randomised trials, case studies) are available analysing the beneficial and harmful effects of cannabis, cannabinoids, and CBM, these should be interpreted with caution as they are highly susceptible to bias and cannot provide a reliable evidence-base on which to translate into practice.

In conclusion, the RCT evidence base for using cannabinoids, cannabis and CBM is of low or very low quality, and we found very few beneficial effects of the

drugs or strains that have been tested to date for people with pain. As with any known analgesic, it is unlikely that cannabinoids, cannabis or CBM will reduce pain for everyone. However, they may work for a small number of people, under the close supervision of specialists. High quality trials of other cannabinoids or CBM that have not been tested in clinical trials may provide more answers.

Changes to protocol: We combined 30% reduction in pain intensity and moderate improvement in pain intensity, and 50% reduction in pain intensity and substantial pain improvement in the methods. Both these assessments report the same outcome. We added the risk of bias domain 'size' to the review, which was not outlined in the protocol. We chose to do this due to the risk of bias of smaller studies in analyses. For transparency and comprehensiveness, to allow easy access to a summary, we extracted and reported mean change scores in Appendix 6, and we extracted and reported data but did not analyse them from studies with n<30 in Appendix 4.

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Conflict of interests

- Drs Fisher, Fogarty, Krane, and Moore have nothing to declare.
- Christopher Eccleston reports grants from Versus Arthritis, MayDay Foundation, Cochrane, NIHR outside of submitted work.
- David P. Finn - Dr. Finn reports grants from Alkermes Inc and Shionogi Ltd, outside the submitted work.
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- Andrew Rice – Prof. Rice is a Council Member of IASP and Chair of the Presidential Task Force of the IASP, He undertook consultancy and advisory board work for Imperial College Consultants- in the last 24 months this has included personally remunerated work outside of the submitted work for: Pharmanovo, Lateral, Novartis, Pharmaleads, Mundipharma, Orion, Toray, Abide, Asahi Kasei & Theranexis. He was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued between 2015 and 2019 upon the acquisition of Spinifex by Novartis. Prof Rice is a named inventor on the patents – Rice A.S.C, Vandevoorde S. and Lambert D. M Methods using N-(2propenyl)hexadecanamide and related amides to relive pain. WO2005/079771 pending, and Okuse K. et al Methods of treating pain by inhibition of vgf activity EP13702262.0/WO2013110945 pending. During the conduct of the study Imperial College received grants funding to support

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References

[1] Andresen SR, Bing J, Hansen RM, Biering-Sorensen F, Johannesen IL, Hagen EM, Rice ASC, Nielsen Jo F, Bach FW, Finnerup NB. Ultramicronized palmitoylethanolamide in spinal cord injury neuropathic pain: A randomized, double-blind, placebo-controlled trial. Pain 2016;157(9):2097-2103.

[2] Ball S, Vickery J, Hobart J, Wright D, Green C, Shearer J, Nunn A, Cano MG, MacManus D, Miller D, et al. The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health Technol Assess 2015;19(12):1-187.

[3] Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: Results of a randomised controlled trial. Pain 2004;112(3):299-306.

[4] Bradford D, Stirling A, Ernault E, Liosatos M, Tracy K, Moseley J, Blahunka P, Smith MD. The MOBILE Study-A Phase IIa enriched enrollment randomized withdrawal trial to assess the analgesic efficacy and safety of ASP8477, a fatty acid amide hydrolase inhibitor, in patients with peripheral neuropathic pain. Pain Med 2017;18(12):2388-2400.

[5] Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, Notcutt W, O'Leary C, Ratcliffe S, Nováková I, Zapletalova O, Piková J, Ambler Z. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res 2010;32(5):451-459.

[6] Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, Gouaux B. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ 2012;184(10):1143-1150.

[7] Costa B, Giagnoni G, Franke C, Trovato AE, Colleoni M. Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. Br J Pharmacol 2004;143(2):247-250.

[8] Cruccu G, Stefano GD, Marchettini P, Truini A. Micronized Palmitoylethanolamide: A Post Hoc Analysis of a Controlled Study in Patients with Low Back Pain - Sciatica. CNS Neurol Disord Drug Targets 2019;18(6):491-495.

[9] Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, Kerns R, Von Korff M, Porter L, Helmick C. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:1001–1006.

[10] Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. BMJ 2013;346:f2304.

[11] Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, Rodriguez V, Jongsma HE, Ferraro L, La Cascia C, La Barbera D, Tarricone I, Berardi D, Szöke A, Arango C, Tortelli A, Velthorst E, Bernardo M, Del-Ben CM, Menezes PR, Selten JP, Jones PB, Kirkbride JB, Rutten BP, de Haan L, Sham PC, van Os J, Lewis CM, Lynskey M, Morgan C, Murray RM, Group E-GW. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry 2019;6(5):427-436.

[12] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9(2):105-121.

[13] Eccleston C, Fisher E, Cooper T, Grégoire MC, Heathcote L, Krane E, Lord S, Sethna N, Anderson AK, Anderson B, Clinch J, Gray AL, Gold JI, Howard R, Ljungman G, Moore R, Schecther N, Wiffen P, Wilkinson NR, Williams D, Wood C, van Tilburg M, B. Z. Pharmacological interventions for chronic pain in children and adolescents: An overview of systematic reviews. in submission.

[14] Eccleston C, Malleson P. Managing chronic pain in children and adolescents. BMJ 2003;326(7404):1408-1409.

[15] Faig-Marti J, Martinez-Catassus A. Use of palmitoylethanolamide in carpal tunnel syndrome: a prospective randomized study. J Orthop Traumat 2017;18(4):451-455.

[16] Fallon MT, Albert Lux E, McQuade R, Rossetti S, Sanchez R, Sun W, Wright S, Lichtman AH, Kornyeyeva E. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. Br J Pain 2017;11(3):119-133.

[17] Fanelli D, Costas R, Ioannidis JP. Meta-assessment of bias in science. Proc Natl Acad Sci USA 2017;114(14):3714-3719.

[18] Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open 2016;6(6):e010364.

[19] Fisher E, Eccleston C, Degenhardt L, Finn DP, Finnerup NB, Gilron I, Haroutounian S, Krane E, Rice ASC, Rowbotham M, Wallace M, Moore RA. Cannabinoids, cannabis, and cannabis-based medicine for pain management: a protocol for an overview of systematic reviews and a systematic review of randomised controlled trials. Pain Rep 2019;4(3):e741.

[20] Frank B, Serpell MG, Hughes J, Matthews JNS, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ 2008;336(7637):199-201.

[21] Gilron I, Blyth F, Degenhardt L, DiForti M, Eccleston C, Haroutounian S, Moore RA, Rice A, Wallace M. Risks of harm with cannabinoids, cannabis, and cannabis-based medicine for pain management relevant to patients receiving pain treatment: Protocol for an overview of systematic reviews. Pain Reports 2019;4(3):e742.

[22] Guida G, De Martino M, De Fabiani A, Cantieri L, Alexandre A, Vassallo GM, Rogai M, Lanaia F, Petrosino S. Palmitoylethanolamide (Normast) in chronic neuropathic pain by compressive type lumbosciatalgia: Multicentric clinical study. DOLOR 2010;25(1):35-42.

[23] Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, Brozek J, Norris S, Meerpohl J, Djulbegovic B, Alonso-Coello P, Post PN, Busse JW, Glasziou

P, Christensen R, Schunemann HJ. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 2013;66(2):158-172.

[24] Guyatt GH, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, Atkins D, Kunz R, Montori V, Jaeschke R, Rind D, Dahm P, Akl EA, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol 2013;66(2):151-157.

[25] GWPharmaceuticals Ltd. A double blind, randomised, placebo controlled, parallel group study of Sativex in the treatment of subjects with pain due to diabetic neuropathy (EUCTR2004-002530-20). EU Clinical Trials Register. Accessed March 2020.

[26] GWPharmaceuticals Ltd. A study of sativex. for pain relief due to diabetic neuropathy (NCT00710424), Accessed March, 2020.

[27] Hauser W, Finn DP, Kalso E, Krcevski-Skvarc N, Kress HG, Morlion B, Perrot S, Schafer M, Wells C, Brill S. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain 2018;22(9):1547-1564.

[28] Henrich J, Heine SJ, Norenzayan A. The weirdest people in the world? Behav Brain Sci 2010;33(2-3):61-83:83-135.

[29] Higgins JPT, Altman DG, Sterne JACe. Chapter 8: Assessing risk of bias in included studies In: JPT Higgins, R Churchill, J Chandler, MS Cumpston, editors. Cochrane Handbook for Systematic Reviews of Interventions version 520 (updated June 2017): Cochrane, 2017.

[30] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Intervetnions Version 5. 1. 0: The Cochrane Collaboration, 2011.

[31] Iannotti FA, Hill CL, Leo A, Alhusaini A, Soubrane C, Mazzarella E, Russo E, Whalley BJ, Di Marzo V, Stephens GJ. Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. ACS Chem Neurosci 2014;5(11):1131-1141.

[32] Jochimsen PR, Lawton RL, VerSteeg K, Noyes Jr R. Effect of benzopyranoperidine, a DELTA-9-THC congener, on pain. Clinical Pharmacology and Therapeutics 1978;24(2):223-227.

[33] Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Sympt Man 2010;39(2):167-179.

[34] Kalliomaki J, Segerdahl M, Webster L, Reimfelt A, Huizar K, Annas P, Karlsten R, Quiding H. Evaluation of the analgesic efficacy of AZD1940, a novel cannabinoid agonist, on post-operative pain after lower third molar surgical removal. Scandinavian Journal of Pain 2013;4(1):17-22.

[35] Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, Ratcliffe S. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol 2013;260(4):984-997.

[36] Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol 2015;172(20):4790-4805.

[37] Leocani L, Nuara A, Houdayer E, Schiavetti I, Del Carro U, Amadio S, Straffi L, Rossi P, Martinelli V, Vila C, Sormani MP, Comi G. Sativex(®) and clinical-neurophysiological measures of spasticity in progressive multiple sclerosis. J Neurol 2015;262(11):2520-2527.

[38] Levin DN, Dulberg Z, Chan AW, Hare GMT, Mazer CD, Hong A. A randomized-controlled trial of nabilone for the prevention of acute postoperative nausea and vomiting in elective surgery. Can J Anesth 2017;64(4):385-395.

[39] Lichtman AH, Lux EA, McQuade R, Rossetti S, Sanchez R, Sun W, Wright S, Kornyeyeva E, Fallon MT. Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. J Pain Sympt Man 2018;55(2):179.

[40] Markova J, Essner U, Akmaz B, Marinelli M, Trompke C, Lentschat A, Vila C. Sativex as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. Int J Neurosci 2019; 129(2):119-128.

[41] McAteer A, Elliott AM, Hannaford PC. Ascertaining the size of the symptom iceberg in a UK-wide community-based survey. Br J Gen Pract 2011;61(582):e1-11.

[42] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

[43] Mohiuddin M, Blyth FM, Degenhardt L, Di Forti M, Eccleston C, Haroutounian S, Moore RA, Rice ASC, Wallace M, Park R, Gilron I. Risks of harm with cannabinoids, cannabis, and cannabis-based medicine relevant to patients receiving pain treatment: an overview of systematic reviews. Under review.

[44] Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev 2015(7):CD008242.

[45] Moore RA, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. BMJ 2013;346:f2690.

[46] Moore RA, Derry S, Wiffen PJ, Banerjee S, Karan R, Glimm E, Wiksten A, Aldington D, Eccleston C. Estimating relative efficacy in acute postoperative pain: network meta-analysis is consistent with indirect comparison to placebo alone. Pain 2018;159(11):2234-2244.

[47] Moore RA, Fisher E, Finn DP, Finnerup NB, Gilron I, S. H, Krane E, Rice ASC, Eccleston C, Rowbotham M, Wallace M. Cannabinoids, cannabis, and cannabis-based medicine for pain management: an overview of systematic reviews. Under review.

[48] NCT01606176. A Study to Evaluate the Effects of Cannabis Based Medicine in Patients With Pain of Neurological Origin.

[49] NCT01606202. A Study of Cannabis Based Medicine Extracts and Placebo in Patients With Pain Due to Spinal Cord Injury. Https://clinicaltrialsgov/show/nct01606202 2012.

[50] Nosek BA, Alter G, Banks GC, Borsboom D, Bowman SD, Breckler SJ, Buck S, Chambers CD, Chin G, Christensen G, Contestabile M, Dafoe A, Eich E, Freese J, Glennerster R, Goroff D, Green DP, Hesse B, Humphreys M, Ishiyama J, Karlan D, Kraut A, Lupia A, Mabry P, Madon TA, Malhotra N, Mayo-

Wilson E, McNutt M, Miguel E, Paluck EL, Simonsohn U, Soderberg C, Spellman BA, Turitto J, VandenBos G, Vazire S, Wagenmakers EJ, Wilson R, Yarkoni T. Scientific standards. Promoting an open research culture. Science 2015;348(6242):1422-1425.

[51] Noyes R, Jr., Brunk SF, Avery DA, Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clinical Pharmacology and Therapeutics 1975;18(1):84-89.

[52] Nuesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, Egger M, Juni P. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. BMJ 2010;341:c3515.

[53] Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain 2007;133(1-3):210-220.

[54] Ostenfeld T, Price J, Albanese M, Bullman J, Guillard F, Meyer I, Leeson R, Costantin C, Ziviani L, Nocini PF, et al. A randomized, controlled study to investigate the analgesic efficacy of single doses of the cannabinoid receptor-2 agonist GW842166, ibuprofen or placebo in patients with acute pain following third molar tooth extraction. Clin J Pain 2011;27(8):668-676.

[55] Owens B. Drug development: The treasure chest. Nature 2015;525(7570):S6-8.

[56] Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol 2008;153(2):199-215.

[57] Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, McQuade R, Wright S, Fallon MT. Nabiximols for opioid-treated cancer

patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain 2012;13(5):438-449.

[58] Rice AS, Smith BH, Blyth FM. Pain and the global burden of disease. Pain 2016;157(4):791-796.

[59] Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65(6):812-819.

[60] Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res 2005;30(8):1037-1043.

[61] Ryberg E, Larsson N, Sjögren S, Hjorth S, Hermansson NO, Leonova J, Elebring T, Nilsson K, Drmota T, Greasley PJ. The orphan receptor GPR55 is a novel cannabinoid receptor. Br J Pharmacol 2007;152(7):1092-1101.

[62] Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients. European Neurology 2017;78(5-6):320-329.

[63] Seeling W, Kneer L, Buchele B, Gschwend J, Maier L, Nett C, Simmet T, Steffen P, Schneider M, Rockemann M. DELTA9-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative pain. Anaesthesist 2006;55(4):391-400.

[64] Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, Ehler E. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain 2014;18(7):999-1012.

[65] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for

systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.

[66] Smith D, Wilkie R, Croft P, McBeth J. Pain and Mortality in Older Adults: The Influence of Pain Phenotype. Arthritis Care Res 2018;70(2):236-243.

[67] Smith D, Wilkie R, Croft P, Parmar S, McBeth J. Pain and mortality: mechanisms for a relationship. Pain 2018;159(6):1112-1118.

[68] Smith SM, Chang RD, Pereira A, Shah N, Gilron I, Katz NP, Lin AH, McDermott MP, Rappaport BA, Rowbotham MC, Sampaio C, Turk DC, Dworkin RH. Adherence to CONSORT harms-reporting recommendations in publications of recent analgesic clinical trials: an ACTTION systematic review. Pain 2012;153(12):2415-2421.

[69] Smith SM, Wang AT, Katz NP, McDermott MP, Burke LB, Coplan P, Gilron I, Hertz SH, Lin AH, Rappaport BA, Rowbotham MC, Sampaio C, Sweeney M, Turk DC, Dworkin RH. Adverse event assessment, analysis, and reporting in recent published analgesic clinical trials: ACTTION systematic review and recommendations. Pain 2013;154(7):997-1008.

[70] Sprangers MA, de Regt EB, Andries F, van Agt HM, Bijl RV, de Boer JB, Foets M, Hoeymans N, Jacobs AE, Kempen GI, Miedema HS, Tijhuis MA, de Haes HC. Which chronic conditions are associated with better or poorer quality of life? J Clin Epidemiol 2000;53(9):895-907.

[71] Starowicz K, Finn DP. Cannabinoids and Pain: Sites and Mechanisms of Action. Adv Pharmacol 2017;80:437-475.

[72] Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, Murnion B, Farrell M, Weier M, Degenhardt L. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and

meta-analysis of controlled and observational studies. Pain 2018;159(10):1932-1954.

[73] Straiker A, Mitjavila J, Yin D, Gibson A, Mackie K. Aiming for allosterism: Evaluation of allosteric modulators of CB1 in a neuronal model. Pharmacol Res 2015;99:370-376.

[74] Wagenlehner FME, van Till JWO, Houbiers JGA, Martina RV, Cerneus DP, Melis JHJM, Majek A, Vjaters E, Urban M, Ramonas H, Shoskes DA, Nickel JC. Fatty Acid Amide Hydrolase Inhibitor Treatment in Men With Chronic Prostatitis/Chronic Pelvic Pain Syndrome: An Adaptive Double-blind, Randomized Controlled Trial. Urology 2017;103:191-197.

[75] Wiffen PJ, Derry S, Bell RF, Rice AS, Tölle TR, Phillips T, Moore RA. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2017;6:CD007938.

[76] Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013;14(2):136-148.

[77] Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008;9(6):506-521.

[78] Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain From Spinal Cord Injury and Disease. J Pain 2016;17(9):982-1000.

[79] Woodhams SG, Chapman V, Finn DP, Hohmann AG, Neugebauer V. The cannabinoid system and pain. Neuropharmacology 2017;124:105-120.

[80] Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, Thompson A, Group UMR. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet (London, England) 2003;362(9395):1517-1526.

[81] Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG, Group MR. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. Journal of neurology, neurosurgery, and psychiatry 2012;83(11):1125-1132.

[82] Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, Moher D, Vohra S, Group P. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ 2016;352:i157.

Figure Legends

Figure 1. PRISMA flow chart of studies

Figure 2. Risk of bias

Figure 3. Risk of bias summary

Figure 4. Analysis 6.1. 30% reduction in pain intensity

Figure 5. Analysis 6.2. 50% reduction in pain intensity

Figure 6. Analysis 6.3. Mean change for pain intensity (0-10 rating scale)